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CONFERENCE ON THE PROBLEM OF ACUTE RADIATION SICKNESS

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CONFERENCE ON THE PROBLEM OF ACUTE RADIATION SICKNESS

/Following is the translation of an article by L.G. Ratgauz entitled "Konferentsiya po Probleme Ostroy Luchevoy Bolezni" (English version above) in Vestnik Akademii Meditsinskikh Nauk SSSR (Herald of the Academy of Medical Sciences USSR) No 2, Feb 60, Moscow, 89-94./

A conference on the problem of "acute radiation sickness and its remote complications" was held 19-21 October 1959 in the Institute of Experimental Pathology and Therapy of the Acad Med Sci USSR, in Sukhumi. Participating in the conference were research workers of the Scientific Research Institutes of Moscow, Sukhumi, Khar'kov, Tbilisi, Yerevan, Leningrad, as well as guests from the United States -- six radiologists from various radiological laboratories.

The basic problems at the conference were: a) particularities of the course of acute radiation sickness in monkeys, b) problems of changes in the radiosensitivity of mammals under the influence of the administration of various substances, c) infectious complications in acute and chronic radiation sickness, d) remote complications of acute radiation sickness.

In opening the conference, Professor V.N. Orekhovich, academician and secretary of the Department of Medical and Biological Sciences of the A.M.S. USSR, stressed that the first conference of the Institute of Experimental Pathology and Therapy testified to its creative growth. Of the 16 reports that were to be heard during the conference, seven were to be presented by the co-workers of this institute.

In the report about the clinical picture of radiation sickness in monkeys, L.F. Semenov emphasized that a special place in the experimental study of the disease belongs to the reproducibility of this process in monkeys. There are not many works devoted to radiation sickness in monkeys. The author has studied various types of reactions of monkeys to a single massive irradiation, as well as to the clinical picture of acute radiation sickness. The tests were performed on 219 Macacae and 23 hamadrill baboons. All

animals were subjected to irradiation by a "RUM-3" X-ray apparatus as well as by an experimental cobalt gamma-irradiator with a charge of 4000 curies. Hematological, biochemical and physiological methods were used in the observations, followed by histological studies of some organs and tissues of the dead animals.

As a result of these studies conditions were established for the development of radiation sickness depending on the magnitude of the irradiation dose. Acute radiation sickness in monkeys revealed a basic similarity with radiation sickness of other mammals; it had the same basic symptoms, syndromes and pathogenetic mechanisms.

During the course of radiation sickness in monkeys, this is what is observed: a) the period of early reaction (24-36 hours after irradiation), b) the first period of the main process -- predominance of the areactive state (second to eighth day), c) second period predominance of the reactive process (eighth to 20th day), d) restoration period (20th to 30th day), a characteristic mark of this period is incomplete recovery from all the systemic disturbances (this continues for another $1\frac{1}{2}$ - 2months). The process undergone by the organism may, however, leave permanent defects or cause the development of remote complications.

Whereas the main symptoms of radiation sickness in monkeys are similar to those in other varieties of mammals there are some individual peculiarities of this process in monkeys;

1. the early reaction manifests itself much sonner than in other mammals, however, shock, as happens in rabbits, is never observed.
2. lesions of the hemopoetic system develop slowly; leucopenia reaches its peak on the eighth to 10th day.
3. the intestinal syndrome of acute radiation sickness develops slowly.
4. the hemorrhagic syndrome has a very stormy course with more serious symptoms than in other mammals.
5. the infectious phase (third to fourth week) is just as pronounced as in other mammals.

By comparing acute radiation sickness in monkeys and other mammals with the clinical picture of this affliction in man, the author came to the conclusion that radiation sickness in monkeys is the closest experimental model of acute radiation sickness in humans.

Data on changes of the vascular system during acute radiation sickness as well as in the late periods after the action of penetrating radiation were presented in the report of A.V. Lebedinskiy and V.V. Yakovlev on the influence of ionizing radiation on the cardiovascular system of monkeys.

The authors studied 33 monkeys, 20 of which once had had acute radiation sickness and 13 were used as controls. The great stability of the pletysmogram of arterial pressure and tonus testifies to fact that in monkeys previously subjected to irradiation the reactivity of the vessels was considerably reduced. Changes in arterial pressure and arterial tonus were more pronounced in animals which had received over 600r as compared to monkeys irradiated with smaller doses.

Parallel with these experiments, the authors studied the condition of the vascular system during acute radiation sickness in 33 monkeys.

After irradiation the arterial pressure decreased in all experimental animals. The tonus of the arteries increased. The state of the vessels was of a spastic character. In order to explain the degree and depth of the vascular spasm, the authors used a heat stimulant which produced some vasodilation and lowering of the arterial tonus.

On the basis of their investigations the authors came to the conclusion that vaso-constriction was a compensatory factor favoring equalization of arterial pressure. The lowering of blood pressure they consider to be a result of dilation of the vessels of the internal organs.

The report of N.A. Krayevskiy and A.S. Petrova "Changes of the hemopoetic organs in Macacae rhesus during acute radiation sickness" showed that the structure of the hemopoetic organs and the composition of the peripheral blood in this species of monkeys are close to those of human beings.

Much more marked changes in the quantitative and qualitative blood indices appear in monkeys during acute radiation sickness as compared to other animals. For example, in monkeys the number of leucocytes sometimes reaches 90,000 per cubic mm. of blood with a considerable rejuvenation of the cellular composition shifting towards promyelocytes. Hypersegmentation and anisocytosis of the neutrophiles and microcytosis of the blood platelets appear early. Progressive "emptying" of the bone marrow with depression of the red, white, and megocaryocytary growth takes place. At the same time manifestations of regeneration in monkeys become apparent very early when symptoms of disturbance of the course of physiological regeneration are present.

The authors noted considerable resorptive changes of the bone tissues, a fact which indicates the high reactivity of this species of monkeys.

In the report, "Morphological changes of the central nervous system in monkeys in acute radiation sickness", A.F. Bibikova presented data of studies of the central nervous

systems in eight monkeys after a single total irradiation with a dose of 624r. The author found changes in the neurons, elements of the glia, as well as in the vessels.

The pathological changes were characterized by edema of the brain tissue, occasional perivascular and pericellular edema, foci of missing nerve cells in the cerebral cortex as well as in lower subcortical structures, focal demyelinization, diffuse proliferative-degenerative reaction of the microglia, focal degeneration of the ologodendroglia and weak proliferative reaction of the astrocytary glia.

"Some biochemical changes in monkeys subjected to the influence of ionizing radiation" was the title of the report by S.S. Vasileyskiy, N.N. Demin, N.V. Korneyeva, M.A. Lomovaya, and L.I. Polikarpova. They spoke on determinations of sulfhydryl groups, components of adenylic acids, ascorbic and dehydroascorbic acid, acetylcholine and cholinesterase activity in some tissues of monkeys during acute radiation sickness and one to three years after irradiation. In addition, the content of the sulfhydryl groups and thioprotein fractions and the cholinesterase activity in the blood were studied.

The authors detected a number of regular changes occurring also in animals with remote sequelae of acute radiation sickness fron which they recovered.

The rate of regeneration of proteins and nucleic acids in the hemopoetic organs during total irradiation by X-rays of guinea pigs (400r dose) and rabbits (600r dose) was studied by Ye.A. Dikovenko and B.V. Blinov. The indicator of regeneration was the rapidity with which P^{32} and tagged amino acids, introduced during various periods after irradiation, entered the proteins and nucleo-proteids. The condition of hemopoesis was judged by the blood picture, inclusion of Fe^{59} in the errythrocytes, weight and histological structure of the spleen.

The studies performed by the authors showed that irradiated animals show a marked inhibition of metabolism of nucleic acids in the bone marrow and spleen. The most important biochemical change characterizing the condition of hemoposis during various stages of the development of acute radiation sickness is the change in the metabolism of nuceic acids.

The reactivity of the hemopoetic system of irradiated animals with regard to agents which, under normal conditions, cause an acute leucocytary reaction (milk, morphine, phenamine, adrenaline and others) underwent wave-like changes.

The author's analysis of the mechanism of the change in the reactivity of the hemopoetic system with regard to stimulating influences showed that it depended on the condition of the central nervous system and mainly on that of the subcortical centers.

B.A. Fedorov reported on the condition of the adrenals during various forms of radiation sickness. The author showed that during acute radiation sickness an increased function of the adrenals is evident. This reaction appears as early as the first hours after irradiation and manifests itself in various degrees depending on the gravity of radiation sickness, and is enhanced by protective prophylactic agents -- betamercaptoethylamin and adrenaline with acetylcholine. Even large doses of radiation (10,000 to 12,000r) cannot prevent the active function of the adrenals. Removal of the adrenals increases the severity of the course of radiation sickness. The author assumes that the increased function of the adrenals in radiation sickness may well be an essential part of the compensatory protective reactions developing in the organism.

"Species differences in the reaction of the properdin system and serotonin in radiation injuries" was the subject of the report by A.A. Bagdasarov, M.O. Raushenbakh, I.L. Chertkova, and G.A. Chernova. The authors showed that different species of animals show individual reactions of the properdin system to the influence of ionizing radiation. The results of investigations showed that irradiation does not influence the synthesis of properdin and that the decrease in properdin apparently can be explained by its being bound to mucopolysaccharids, the blood content of which increases parallel to the decrease of properdin during acute radiation injuries.

As far as serotonin is concerned, two types of changes in its blood content during acute radiation sickness were found in the animals studied.

1. in monkeys, dogs, guinea pigs, and rabbits there was an abrupt and profound drop in the level of serotonin in whole blood, which sometimes coincided with the peak of the hemorrhagic syndrome.

2. in rats and mice no substantial changes of the serotonin content of the blood could be detected after irradiation.

The study of the changes of serotonin in the small intestine and the brain of guinea pigs and rats showed that under the influrence of irradiation there is a phasic change in the serotonin content of these organs.

A decrease in the quantity of serotonin in the blood during acute radiation sickness is apparently caused by interference with serotonin formation in the body rather than by the acceleration of its destruction. R.V. Petrov, A.S. Petrova, N.L. Melik-Pashayeva, and V.V. Shikhodyrov reported on the appearance of C-reactive protein (CRP) in the blood of humans and apes under the influence of ionizing radiation.

By means of immunodiagnosis with CRP antiserum, the authors studied the blood of 56 persons. Radiation (X-rays) was administered to an area afflicted by a neoplastic process. In several cased the authors detected CRP after irradiation. In order to clarify the question of radiation injury as a cause of the appearance of CRP in the blood, experiments were conducted on monkeys irradiated with gamma rays. The authors found the maximum quantity of CRP in the blood as early as the next day.

The authors believe that CRP appears in the blood under the influence of radiation injury. The diagnostic and prognostic importance of the determination of this protein is subject to further investigation.

Another series of reports was devoted to changes in the radiosensitivity of mammals under the influence of the administration of various substances.

"The mechanism of the radioprotective influence of some aminoethyl derivatives" was reported by P.G. Zherebchenko, Ye.S. Golovchinskaya, P.G. Kostyanovskiy, N.G. Krasnykh, M.N. Shchukina and others. The authors synthesized several aminoethyl derivatives of indol, phenol, indazol, aniline, purine, and pyramidine bases and studied their radioprotective properties. Preparations were discovered among these substances that possess the ability to decrease the severity of radiation injuries when used prior to irradiation.

In experiments on mice, data were obtained on the effect of aminoethyl derivatives upon the amount of oxygen consumption and the body temperature of intact animals to whom monoaminoxidase inhibitors had previously been administered.

The report of P.G. Zherebchenko, I.G. Krasnykh, N.P. Levkov, and S.P. Yarmonenko was devoted to the protective influence of local asphyxia of the bone marrow in acute radiation sickness of animals.

On the basis of data concerning the beneficial influence on the course and end result of radiation injuries by transplants of hemopoetic tissues and also by taking into consideration the possibility of decreasing radiosensitivity of tissues by creating local hypoxia, the authors studied the influence of local asphyzia of the bone marrow on the course and end result of radiation injury. Asphyxia of the bone marrow of an extremity is created by means of a tourniquet -- which is applied immediately before the beginning of irradiation and removed as soon as it is terminated. The authors ascertained a substantial increase in the survival and prolongation of life of the animals and also learned about the influence of local asphyxia of the bone marrow in combination with the protective action of merkamin and antibiotics on the course and end result of radiation sickness.

L.F. Semenov, V.D. Lyashenko, F.Yu. Paginskiy, I.B. Simon, N.N. Suvorov, and M.N. Shchukina reported on the prevention of radiation sickness in lower mammals and monkeys. The speakers reported that the investigations were directed towards the study of agents changing the condition of the organism at the moment of irradiation which might have a protective antiradiation effect.

Comparison of the protective action of the preparations with their physiological effect andcomparison of the antiradiation effect with the chemical structure of protective substances were the main methods of investigation.

The bulk of the study was conducted on 40 thousand white mice. Affirmative results were verified on rats, cats, and guinea pigs (2,000 animals). The most effective protective agents in acute radiation sickness were tested on 150 monkeys.

Radiation sickness was produced by irradiation with X-rays or gamma rays from radioactive cobalt. The protective action was evaluated on the basis of survival of the animals after an absolute lethal dose of radiation and the decreased severity of the basic symptoms of radiation sickness. Among the many tested agents a marked protective effect was produced by histamine, adrenaline serotonin, and acetylcholine (survival rate 12-25 percent). This effect was markedly increased by combining peripheral neurotropic agents (survival rate 40-75 percent). Combinations of adrenaline histamine, or serotonin with acetylcholine proved effective. According to the authors, the combination of serotonin with acetylcholine (survival rate 75-80 percent) was the strongest of all the protective means that they had studied.

Among the several sulfur-containing agents studied, the most effective proved to be cystein (survival rate 15 percent), betamercaptoethylamin (survivalrate 20 percent), its disulfate (survival rate 22 percent), and thiurea (survival rate 25 percent).

All protective preparations reveal certain typical effects in their action on a nonirradiated organism. In experiments on monkeys the protective action of betamercaptoethylamin and the combinations of adrenaline with acetylcholine and tryptamin with acetylcholine were checked and confirmed. These preparations resulted in a survival rate of 20 to 25 percent in the presence of a 100 percent lethal dose.

The authors believe that combinations of adrenaline (and its analogues) or serotonin (and its analogues) with acetylcholine and other M-cholinergic preparations are most promising for practical use.

B.A. Lapin and S.A. Romanova reported on the effect of some endocrine factors upon the radiosensitivity of animals. The species showed that the resistance of these animals to the influence of penetrating radiation increased as a result of the administration of estrogens to white male mice and rats; diethylstybestrolpropionate and synestrol have the most pronounced effect (the survival rate reaches 25 percent as compared to 100 percent mortality in the controls). In females this effect was very insignificant. This protective effect was not observed in sexually immature animals (males and females).

Castration of male white mice and white rats, one month prior to irradiation, increases the resistance of these animals to the influence of ionizing radiation (survival rate of white mice 14.3 percent, white rats 27.1 percent as compared to 100 percent mortality in the controls). Spaying of females increases resistance to the influence of radiation very negligibly.

In the report "The impoertance of infectious complications on the outcome of radiation sickness produced in monkeys by fractionized irradiation", E.K. Dzhikidze and A.S. Aksenova reported on the role of these complications in radiation sickness, reproducible under repeated exposure to ionizing radiation.

The lowering of the natural resistance of the monkey's organism takes place against the background of progressive radiation injury. This creates conditions for the activation of latent infections. These infectious complications make the basic diseases more serious. In a series of experiments, in which chemotherapy was used with the aim of preventing infectious complications, the authors were able to show its importance in the outcome of radiation sickness.

Professor V.L. Troitskiy reported on the subject, "Increase of the natural immunity of irradiated animals by stimulating hemopoesis".

The speaker discussed the importance of stimulating hemopoesis as a basis for the increase in natural immunity that was interfered with by irradiating the animals with gamma rays. Two methods of stimulating hemopoesis in irradiated animals are possible: the introduction of bone marrow cells or lymphocytes from normal animals and the induction of myeloid tissue formation outside the bone marrow.

Intravenous injection of bone marrow cells or lymphocytes into irradiated rats and mice protects a considerable number of these animals from destruction. The combined use of chemotherapy and bone marrow exerts a beneficial clinical effect -- it brings hemopoesis back to normal. Administration

of bone marrow stimulates the natural resistance of the animals and restores inoculation immunity to a large degree.

The speaker dwelled upon the ectoptic formation of bone and extramedullary hemopoesis in the normal organism, which take place by induction from connective cells under the influence of transplants of transitional epithelium.

In guinea pigs irradiated with doses causing destruction of their bone marrow, the capacity of extramedullary formation of myeloid tissue is preserved under the influence of transitional epithelium. "By this means," said the speaker, "it is possible to produce myeloid cells in the irradiated organism from the organism's own cells".

Ye. A. Dikovenko reported on the delayed sequelae of acute radiation sickness in monkeys. The speaker analyzed the results of observations on 59 monkeys who had undergone acute radiation sickness, 32 of which were irradiated with doses of 550-700r and 27 with doses of over 400r. During the period of observation (beginning in 1956), 14 monkeys died: seven of them, irradiated with doses of 400r, died of tuberculosis four to six months after irradiation and the remaining seven of pneumonia, dysentery, acute cardiovascular insufficiency, and gastric ulcer. In four of these seven monkeys, autopsy revealed a marked atrophy of the bone marrow, spleen, and lymph nodes.

The general condition of the surviving monkeys is satisfactory. Research has shown the presence of disturbances in the procreative functions, a tendency towards the hypertensive state, decreased function of the thyroid gland and weakened reactivity, particularly in the hemopoetic system. The latter deserves attention as one of the possible sources of diseases of the hemopoetic system a long time after irradiation. The increase in blood pressure and vascular tonus concomitent with decrease of thyroid function could be an indication of early sclerotic changes in the blood vessels.

In addition to the reports specified in the program of the conference, there were three reports given by our guests from the United States.

Professor D. Pickering reported observations in monkeys on the penetration of radioactive strontium and calcium in pregnant animals from the maternal organism into the organism of the embryo. These facts are of great practical value and indicate the necessity of great care while working with radioactive preparations during pregnancy.

Professor T. Curtis showed that various chemical poisons (down to nitrogen yperites) or bacterial and viral toxins do not decrease the life span of mice after the period of acute disease. However, the influence of radiation, whether in massive or in small (chronic) doses, considerably shortened the life span of experimental snimals.

Analyzing the causes of death of irradiated chicks during the first day of life, Professor O. Bruce pointed out the role of disturbances in the kidney function and metabolism of nucleic acids and uric acid.

Critical evaluation of the reports presented at the conference took place in a lively and businesslike atmosphere Professor V.L. Troitskiy underlined the importance of studying acute radiation sickness in monkeys, noted the basic similarity of this process in monkeys and man, and indicated the prognostic value of white blood data at the height of the diseases and during the period of recovery.

The author recommended a more detailed study of the vitamin balance in the second half of radiation sickness, as according to his experimental data, the vitamin metabolism in irradiated monkeys is considerably affected.

Professor N.V. Sergeyev recommended that, during the study of radiation sickness in monkeys, greater attention be paid to the analysis of complications, stressing the desirability of the bacteriological characterization of pneumonia.

L.G. Sherman called for a more detailed study of the mechanism of vascular disturbances that had been presented in the report of A.V. Lebedinskiy and V.V. Yakolev and offered an hypothesis of the central (subcortical) origin of their development.

L.F. Semenov dwelled upon the report of M.O. Raushenbakh and his co-authors, mentioning the differences between the serotonin level of the brain and intestine of irradiated rats, which testified to the different role of mediators in the central and peripheral organs.

Discussing the report of L.F. Semyanov, Professor S. Ya. Arbuzov pointed out the possibility of the central mechanism in the protective antiradiation drugs used.

P.G. Zherebchenko stressed the importance of the direct effect upon the tissues of protective aminocompounds and sulfur containing preparations, mentioning their antiradiation action outside the organism.

Professor L.A. Zil'ber stressed that the development of tumors in the irradiated organism may depend, not on the cancerigenic effect of radiation, but on its injurious effect on the vital functions of tissues and cells making them receptive to tumor viruses. Professor G.A. Zedgenidze also pointed to the complex mechanism of the development of tumors after the action of radiation.

B.A. Lapin, the director of the institute, summed up the result of the conference. He spoke of the desirability of studying the question of radiation pathology on monkeys and the delayed consequences of acute and chronic radiation

sickness, as well as the chronic action of small doses of radiation. B.A. Lapin noted the interesting reports of the guests from the United States -- Professors D. Pickering, O. Bruce and T. Curtis.

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